

### REMARKS

Claims 2, 3, 8, 10-13 and 18-21 are pending in the present application and under examination. In the Office Action mailed on October 19, 2006, claims 2-3 were allowed. Claims 8, 10-13 and 18-21 were rejected. Claims 1, 4-7, 9 and 14-17 were canceled.

#### **II. REJECTIONS UNDER 35 USC 112, First Paragraph, Enablement**

Claims 8, 10-13 and 18-21 have been rejected under 35 USC 112, first paragraph, for allegedly failing to enable isolated nucleic acid sequences which have 50% or greater identity to an isolated nucleic acid sequence set forth in SEQ ID NO:3, isolated nucleic acid sequences which encode 10-mer fragments, and isolated nucleic acid sequences which are 80-95% identical to SEQ ID NO:3.

Applicants respectfully traverse the Examiner's rejection and its supporting remarks.

##### A. No prima facie case

The specification must be taken as complying with the first paragraph of § 112 unless there is a reason to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). The Examiner has not provided any reason to doubt that the specification is enabling for making or using of the presently claimed invention. As support for her enablement rejection, the Examiner cites to two articles. As discussed in the previous response, neither of these articles supports a *prima facie* case for lack of enablement of the presently pending claims for the representative use of the claimed nucleic acids for expression of immunogenic polypeptides, as both articles cited by the Examiner relate only to the structural requirements for maintaining biological function, e.g., catalysis of proteins, not to the requirements for an encoded polypeptide having immunogenicity. Section 2164.01(c) of the MPEP states that:

When a compound or composition is limited by a particular use, enablement of the claim should be evaluated based upon that limitation.

In contrast, when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection based upon how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple use are disclosed, the application is enabling for the claimed invention. (citation omitted)

The claimed function and therefore its utility is that the nucleic acid encodes an immunogenic protein. The function of being immunogenic does not rely upon the encoded polypeptide exhibiting its natural biological function. In order to establish a *prima facie* case of lack of enablement, the Examiner must provide evidence that the representative use of expression of an immunogenic polypeptide is not enabled.

The Examiner's response to applicants' argument filed on September 1, 2006 failed to address the underlying assertion that the Examiner had failed to establish that the claims were not enabled. The claims include a function of immunogenicity, not the biological function of the protein in the bacteria. Therefore, the applicants respectfully submit that the Examiner has not cited to any factual support for the assertion that the claims as currently drafted are not enabled because the two articles cited by the Examiner have nothing to do with immunogenicity of proteins, but rather cite to complex biological functions which are not presently claimed. Furthermore, enablement is evaluated as of the filing of the application. Both articles were published well before the priority date of the present application. One article cited by the Examiner, Rudinger *et al.*, is dated 1976, which has no relevance to the state of the art as of the filing date of the present application, which is January 14, 1999. The second article is dated November 1993 and purports to addresses function of two proteins that differ by only a single amino acid. The second article is also irrelevant given that it addresses complex biological function and predates the application by more than five years. Thus, the applicants respectfully assert that the Examiner has not established a *prima facie* case of lack of enablement because none of the articles citing by the Examiner are relevant to the presently claimed function.

B. There is sufficient enablement

Notwithstanding the Examiner's assertions, a careful analysis of the factors announced in *In re Wands* that must be analyzed to determine whether a claim is enabled or undue experimentation would be required to make and use the claim reveals that the Wands factors support the enablement of the pending claims.

1. Predictability

The Examiner appears to believe that a claim is only enabled if one is able to predict the exact sequence of every nucleic acid with the particular use within the claim scope. However, by analogy to the monoclonal antibodies in *In re Wands*, this is not an absolute requirement for enablement, 858 F.2d 731 (Fed. Cir. 1988). Under *Wands*, it is well established that claims to monoclonal antibodies directed to a particular protein are enabled even where the application only discloses the sequence of the protein. Clearly, with just the protein sequence, one of skill in the art could not predict the sequences of even a single monoclonal antibody, much less all monoclonal antibodies that could bind to the protein. Nevertheless, in *Wands*, the Federal Circuit still found such claims to be enabled on the grounds that it is routine for one of skill in the art to immunize an animal such as a rabbit with the protein, generate monoclonal hybridoma from the rabbit and screen them for monoclonal antibodies which are directed to the protein.

The representative use of the presently claimed nucleic acids is analogous to the monoclonal antibodies' function as claimed in *Wands*. In *Wands*, the biological molecules were monoclonal antibodies with the function of binding to HBsAg. With the present claims, the biological molecules are nucleic acids which may be used for expression of an immunogenic polypeptide. Furthermore, as in *Wands*, one of skill can practice the presently claimed invention using routine procedures known to those of skill in the art. To identify sequences that encode immunogenic polypeptides, one of skill need only use a routine procedure of synthesizing nucleotide sequences, expressing the encoded protein using standard expression vectors, and screening polyclonal antibodies obtained from blood of an animal that was immunized with *Neisserial* bacteria for

antibodies that recognize the encoded polypeptide. Screening polyclonal antibodies is a simpler task and even more routine than generating hybridomas and screening monoclonal antibodies produced from them as was found routine and therefore enabled under *Wands*. Thus, under the standard expressed in *Wands*, the present claims are enabled even though the application may not disclose the sequence of every nucleic acid in the present claim scope which will function for the representative use.

Thus, the present claims are enabled because there are well-established, routine methods of screening that will predictably identify nucleic acids for use in expressing immunogenic polypeptides and therefore no undue experimentation is required to determine conditions for use of a nucleic acid within the scope of the claims.

## 2. Amount of Guidance Required

The Examiner has also asserted that the present application lacks sufficient specific guidance regarding which amino acids can be changed while still maintaining the function of the nucleic acids of the invention. As discussed above, this is not relevant to the representative use presently discussed because the use does not require that the protein be functional. The representative use merely requires that some fragment thereof remain immunogenic. Further, working examples are not required to enable an invention. See, *e.g.*, MPEP §2164.02; *In re Borkowski*, 422 F.2d 904, 908 (CCPA 1970). It is well established that guidance need not be provided for the methods if they are readily available to one of skill in the art. See, *e.g.*, MPEP §2164.01 (“A patent need not teach, and preferably omits, what is well known in the art.”). The skill in the art with respect to the presently claimed invention is quite high. These nucleic acids are typically generated by research scientists who are at least Ph.D. level with a fair amount of post-doctoral experience or relevant industry experience. Thus, those of skill in the art are highly capable individuals with a high degree of familiarity with the screening methods needed to identify nucleic acids as claimed.

Further, the application provides ample specific guidance regarding the location of immunogenic epitopes for use in expressing immunogenic polypeptides. On page 48, lines 23 to

28, the specification identifies and provides citations to references describing three well-established methods for identifying antigenic fragments: hydrophilicity plot, antigenic index, and AMPHI analysis. Using these methods, it is routine for one of skill in the art to identify regions that are immunogenic and to avoid making changes in these regions when synthesizing nucleic acids for screening. Applicants further have provided their own hydrophilicity, antigenic index, and AMPHI analysis of SEQ ID NO: 4 in Figure 1E of the specification. Therefore, instead having to randomly determine which nucleic acid substitutions will maintain immunogenicity of the encoded polypeptide, one of skill in the art merely has to look at the provided data and use this as a guide for synthesis of nucleic acids. Finally, the specification discloses *twenty one* sequences that are within the scope of the pending claims as demonstrated by the sequence alignment of the twenty one sequences as shown in Figure 8. This sequence alignment together with the hydrophilicity, antigenic index, and AMPHI analysis provides one of skill in the art a wealth of guidance as to what will be immunogenic and what the conserved regions are within *Neisserial* ORF40s to enable one of skill in the art to make and use the claimed invention.

### 3. Quantity of Experimentation

Contrary to the Examiner's assertions, the expense and time required to identify sequences within the claim scope are irrelevant to the question of whether the experimentation is undue. The expense of experimentation is not one of the Wands factors listed in MPEP §2164.01. Further, MPEP § 2164.06 explicitly states that neither the time nor difficulty of experiments are determinative if they are merely routine. As described in the above section, the screening methods required to practice the claimed invention are routine to those of skill in the art (or at the very least more routine than the screening methods in *Wands* in which the claims were enabled).

As made clear in *In re Wands*, a considerable amount of experimentation is permissible if it is merely routine. 858, F.2d 731 (Fed. Cir. 1988). In *Wands*, the Federal Circuit held that "in the monoclonal antibody art it appears that an 'experiment' is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals

with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics.” 858, F.2d at 740. The Federal Circuit further noted that, “[p]ractitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.” 858, F.2d at 740. The “experiment” of identifying nucleic acids that may be used for either representative use involves design and synthesis of a family of nucleic acids of a particular sequence and then screening for applicability to the use. Therefore, by analogy to monoclonal antibodies, it does not matter that one of skill in the art may have to spend considerable time and expense screening more than one nucleic acid to find one with applicability to the representative use.

The Examiner has asserted that the fact that the claims are direct to nucleic acids rather than proteins would require even more work than if the claims were direct to proteins. However, since the nucleic acid sequence directly corresponds to the expressed protein sequence, no additional work is needed. If the polypeptide sequence is short enough, then the polypeptide may be generated on a peptide sequencer and then screened for activity. One of skill in the art would recognize that the polypeptide generated from the peptide sequencer would have the same activity as the polypeptide generated from expression from the nucleic acid sequence, thus one of skill in the art would not need to generate the nucleic acid to test short sequences. If the polypeptide sequence is too long to generate on a peptide sequencer, then one of skill in the art would have to generate the nucleic acid sequence regardless of whether the claim was to a polypeptide or nucleic acid sequence. Techniques such as site-directed mutagenesis, cassette mutagenesis and even whole gene synthesis with nucleic acid synthesizers has been known and well worked out for over a decade, so generating constructs to test would be quite simple as of the filing date of the present application.

#### 4. Summary

Thus, Applicants respectfully request that the Examiner withdraw the rejection of Claims 8, 12, 13, and 18-21 based upon 35 U.S.C. § 112, first paragraph, enablement. Just as in *Wands*, the presently claimed invention may be practiced by routine screening methods that will allow one of skill in the art to use claimed nucleic acids commensurate in scope for the representative use

discussed above. The guidance in the specification is sufficient given the routine nature of the screening methods to those of skill in the art. The mere fact that the screening methods may be time-consuming and expensive fails to support the Examiner's rejection.

**I. Rejection under 35 U.S.C. § 112, first paragraph, written description**

Claims 8, 10-13 and 18-21 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants respectfully traverse the rejection and its supporting remarks.

**A. No prima facie case**

The specification must be taken as complying with the written description requirement until sufficient evidence or reasoning to the contrary has been presented by the Examiner. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). A general allegation of unpredictability is not sufficient to support a rejection. MPEP §2163.04 (I).

In making the rejection, the Examiner has supplied a citation to Reiger et al., which provides a definition of alleles on page 8 of the Office Action but does not say anything regarding the predictability or lack thereof of the pending claims.

The only other references cited as support for the rejection are three cases, *Fiers v. Revel*, 25 984 F.2d 1164 (Fed. Cir. 1993); *Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991); *The Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997). However, since compliance with the written description rejection is a fact-based inquiry, case law is only relevant to the issue to the extent the facts are similar. In the present application, the claimed invention is to polypeptide fragments of a certain percent identity that are immunogenic. In contrast, in *Fiers*, the claims relate to human fibroblast interferon-beta; in *Amgen*, to erythropoietin; and in *Eli Lilly*, to insulin, in each case as functional proteins. Thus these cases relate to the written description requirements for claiming a protein having a complex biological function, not to the written description requirements for claiming a polypeptide fragment comprising at least one antigenic

determinant, which is significantly more predictable. Furthermore, since the written description requirement is evaluated based upon the factual state of the art as of the priority date of the patent, *Fiers*, *Amgen*, and *Eli Lilly* are also irrelevant to establishing failure to comply with the written description requirement because the priority dates for the patents at issue in *Fiers*, *Amgen*, and *Eli Lilly* were March 19, 1980, November 30, 1984, and May 27, 1977, respectively. The priority date on the present application is October 29, 1999, which is fifteen years after the latest of the three priority dates. In the intervening fifteen years, biochemistry and molecular biology has advanced by leaps and bounds, so what was unpredictable in 1984 is not necessarily still unpredictable in 1999.

As the Office Action makes a general allegation of unpredictability and cites inapplicable cases as the only support for this allegation, Applicants respectfully submit that the Examiner has failed to provide any reasons to doubt that one of ordinary skill would recognize that Applicants had possession of the invention at the time of filing of the application and has therefore failed to make a *prima facie* case for lack of written description.

B. There is sufficient written description

Even assuming that the Examiner has made a *prima facie* case for written description (which is traversed), the rejection is still successfully rebutted by the specification as filed in view of the state of the art at the time of filing.

According to *Eli Lilly*, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See 119 F.3d at 1568, 43 USPQ2d at 1406. In the present application, Applicants have provided description of sufficient number of representative species in two ways – identifying several species by structure and disclosing functional characteristics coupled with a well-established structure-function correlation.



Applicants have disclosed **twenty one** representative species of the claimed genus of an isolated nucleic acid molecule encoding an immunogenic polypeptide having 50% or greater sequence identity to an amino acid sequence of SEQ ID NO:4 by citation of nucleic acid and amino acid structure. Page 65-66 of the specification provides SEQ ID NO: 3 and 4, the nucleic acid sequence and the amino acid sequence of *N. meningitidis*, serogroup B ORF40 protein that is the subject of the presently pending claims. Page 66-67 of the specification provides SEQ ID NO: 5 and 6, the corresponding nucleic acid and amino acid sequence of OFR40 from *N. meningitidis*, serogroup A which exhibits 83.7% sequence identity to SEQ ID NO: 4. Page 65 of the specification provides SEQ ID NO: 1 and 2, the corresponding nucleic acid and amino acid sequence of another OFR40 fragment from *N. meningitidis*, serogroup B which exhibits 65.7% sequence identity to SEQ ID NO: 4. Finally, Example 20 beginning on page 111 of the specification provides amino acid sequences for 14 ORF40s from *N. meningitidis*, serogroup B, 3 ORF40s *N. meningitidis*, serogroup A, C ORF40s *N. meningitidis*, serogroup C, an ORF40 from *N. meningitidis*, serogroup Y and an ORF40 from *N. meningitidis*, serogroup Z. Figure 8 provides a sequence alignment of these twenty one representative sequences.

Applicants also disclose numerous other representative species of the claimed genus by identifying the species by percent sequence identity and antigenicity, a functional characteristic for which there is a well-established correlation between structure and function. Antigenicity is typically determined using software programs which analyze a combination of features including amino acid structure. The computer programs synthesize a vast body of knowledge regarding antigenicity based upon a number of different types of data including empirical evidence of what sequences are antigenic, structural and modeling studies of antigen presenting proteins that reveal the shape of the binding pocket and therefore the consensus sequences for antigens for each antigen presenting protein, and advances in immunology regarding how the immune system responds to novel antigens. By way of example, Figure 1E provides a hydrophilicity plot, an antigenic index, and AMPHI regions for the ORF40 protein that may be combined by one of skill in the art with the sequence alignment of Figure 8 to identify which regions are important for immunogenicity and are conserved. Thus, strong correlations between amino acid structure and antigenicity are well known to those of skill in the art. The Examiner's statements suggest that she believes it is highly

unpredictable whether a particular polypeptide will exhibit antigenicity. In view of the Examiner's citation to case law discussing written description requirements for proteins, it appears that the basis for this belief is an analogy between polypeptide fragments having antigenic function and proteins having more complex biological functions. However, this analogy is inaccurate, as the structural requirements for most biological functions of proteins are much more rigorous than those for antigenic function of polypeptide fragments. For example, protein function typically requires folding in a specific 3-D conformation and certain post-translational modifications. Thus, contrary to the Examiner's belief, there is a strong structure-function correlation between amino acid sequence identity and antigenicity which would allow one of ordinary skill to recognize that Applicants were in possession of the claimed genus.

Thus, in view of the multiple species explicitly disclosed by structure in the specification and the correlation between amino acid structure and antigenic function well known to those of skill in the art (such as the correlation employed by the antigenic determinant prediction software programs disclosed in the specification), one of skill would readily recognize that Applicants had possession of the invention at the time of filing the application.

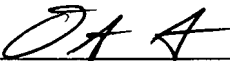
Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 8, 10-13 and 18-21 under 35 U.S.C. § 112, first paragraph, written description.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002099101. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: April 16, 2007

Respectfully submitted,

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